

## REMARKS/ARGUMENTS

Claims 12, 14, 15, and 17-35 are pending in this application. Claims 12 and 14 have been amended and no new matter has been added. Claims 1-11, 13 and 16 have been cancelled either previously or in this Amendment. Claims 12, 14, 15, and 17-34 stand rejected. The issues raised in the Office Action of January 20, 2011 ("Current Action") are as follows:

- \* Claims 12, 14, 18-22, 24-27, and 29-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable; and
- \* Claims 15, 17, and 23 are rejected under 35 U.S.C. § 103(a), as being unpatentable.

In response, Applicant(s) respectfully traverse(s) the outstanding claim rejections and requests reconsideration and withdrawal in light of the remarks presented herein.

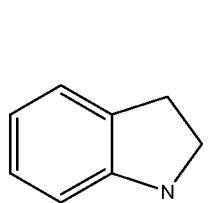
### ***Claims 12, 14, 18-22, 24-27, and 29-34 are rejected under 35 U.S.C. § 103(a)***

The Office Action also rejects claims 12, 14, 18-22, 24-27, and 29-34 as unpatentable under 35 U.S.C. § 103(a) over U.S. Patent Application Publication No. 2002/0058699 to Sweatt et al. (hereinafter Sweatt) and Hall-Jackson et al., in Paradoxical Activation of Raf by a Novel Raf Inhibitor, Chemistry & Biology, August 1999, Vol. 6 pp. 559-568 (hereinafter Hall-Jackson). Applicants respectfully submit that claims 12, 14, 18-22, 24-27, and 29-34 meet the standard of 35 U.S.C. § 103(a). Applicant asserts that the combination of Sweatt and Hall-Jackson fails to establish a *prima facie* case of obviousness.

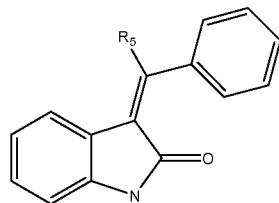
Applicant asserts that the combination of Sweatt and Hall-Jackson does not teach each and every limitation of the instant invention. Specifically, the combination fails to teach an indolone or oxindole composition of any sort, and further fails to teach a 3-substituted indolone (or oxindole). In addition, the combination fails to teach administering to the mammal an effective amount of a 3-substituted indolone that is a C-Raf inhibitor or a pharmaceutically acceptable salt thereof sufficient to reduce neuronal cell death. NOTHING in the combination of Sweatt and Hall-Jackson discloses an indolone (or oxindole).

Sweatt may disclose (but arguably enable) that neuronal excitability, associated with a seizure disorder, may be correlated with increased mitogenactivated protein kinase (MAPK) activity. Hall-Jackson discloses a Benzamide composition. A Benzamide is not an indolone or an oxindole. As such, the combination fails to teach each and every limitation of the instant invention. The combination fails to establish a *prima facie* case of obviousness and the combination fails to provide a suggestion or motivation either in the reference itself, or within the knowledge generally available to one of ordinary skill in the art, to modify the reference; there was no reasonable expectation of success, and all of the claim limitations were not taught or suggested in the prior art references.

Hall-Jackson and the combination fails to teach the same composition or a composition that is even remotely related to the claimed composition. The present invention is an indolone or oxindole as seen below

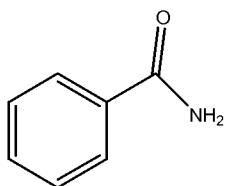


Core indolone

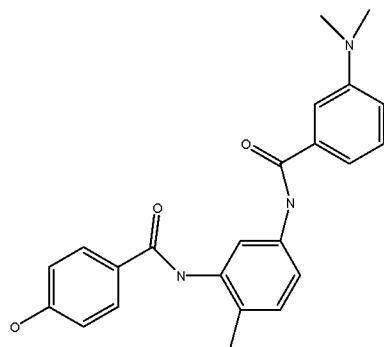


substituted indolone

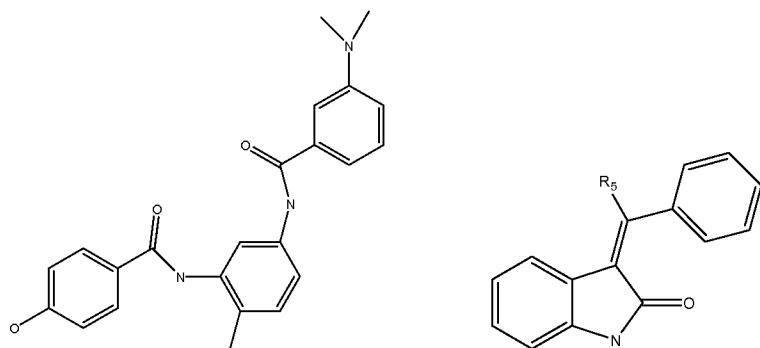
An indolone is an aromatic heterocyclic organic compound with a bicyclic structure, consisting of a six member ring fused to a five member heterocyclic ring with an oxindole having the heteroatom and carbonyl. In stark contrast, the composition of the combination is a Benzamide with the chemical formula of  $C_6H_5CONH_2$  that is a derivative of benzoic acid.



The specific composition disclosed in the combination is (ZM 336372) which is a Benzamide derivative and has the structure:



The Examiner is respectfully asked to provide a reasonable explanation of how a Benzamide related composition can possibly disclose an indolone composition. When viewed side by side (see below) the composition of the combination (ZM 336372) is totally different both structurally and chemically; even the 6 membered rings and carbonyls are different.



ZM 336372

## indolone

It is difficult to find any point of similarity in the composition. The composition of the combination shares no common characteristics with the claimed invention. It is unclear how the Benzamide composition of the combination can teach each and every limitation of the claimed indolone. There is nothing in the knowledge of the skilled artisan that would chemically or physically relate the compositions.

The Office acknowledges on page 12 that the combination fails to teach {5-iodo-3-[(3, 5-dibromo-4-hydroxyphenyl) methylene]-2-indolinone}; however, the combination fails to disclose an indoline or an oxindole at all. As stated on page 12:

Neither Sweatt nor Hall-Jackson expressly teach {5-iodo-3-[(3, 5-dibromo-4-hydroxyphenyl) methylene]-2-indolinone} (herein after GW 5074).

Accordingly, claims 12, 14, 18-22, 24-27, and 29-34 are not rendered obvious from the combination of Sweatt and Hall-Jackson. Applicant respectfully requests the Examiner withdraw the rejection under 35 U.S.C. § 103(a).

***Claims 15, 17, and 23 are rejected under 35 U.S.C. § 103(a)***

The Office Action maintains its rejection of claims 15, 17, and 23 as unpatentable under 35 U.S.C. § 103(a) over Sweatt and Hall-Jackson, and further in view of Varga. Applicant respectfully submits that claims 12, 14, 18-22, and 24-27 meet the standard of 35 U.S.C. § 103(a).

Applicant asserts that the combination of Sweatt and Hall-Jackson and Varga fails to establish a *prima facie* case of obviousness. The Office acknowledges on page 12 that the combination fails to teach {5-iodo-3- [(3, 5-dibromo-4-hydroxyphenyl) methylene]-2-indolinone}. Applicant asserts for the reasons stated above and incorporated herein by reference the combination of Sweatt and Hall-Jackson fails on all counts to establish a *prima facie* case of obviousness. The addition of Varga, does not cure these deficiencies.

The present invention claims a method of reducing apoptotic neuronal cell death in a mammal, by identifying a mammal having one or more apoptotic neuronal cells; administering to the mammal an effective amount of a C-Raf inhibitor that is a 3-substituted indolone, or a pharmaceutically acceptable salt thereof. There is nothing in the combination that teaches identifying a mammal having one or more apoptotic neuronal cells and administering to the mammal an effective amount of a C-Raf inhibitor that is a 3-substituted indolone.

The combination fails to disclose a treatment for individuals susceptible to neurodegenerative diseases. The Office Action argues that it would have been obvious to one of ordinary skills in the art to employ the specific c-Raf of GW 5074 for the treatment of individuals susceptible to neurodegenerative diseases and states one would be motivated to employ GW 5074 because GW5074 is a c-Raf inhibitor as taught by Varga and everyone is susceptible for neurodegenerative disease and would benefit from the administration of GW 5074.

Applicant disagrees that everyone is susceptible for neurodegenerative disease and would benefit from the administration of GW 5074. Applicant asserts that there is nothing in the combination that teaches identifying a mammal having one or more apoptotic neuronal cells; administering to the mammal an effective amount of a C-Raf inhibitor that is a 3-substituted indolone. In fact, there is nothing in the combination that discloses the treatment of a **neurodegenerative** disease in general. Neurodegenerative diseases are a subset of neurological diseases characterized by an abnormal loss of neurons. For example, epilepsy is a neurological disease but not a neurodegenerative disease. Epilepsy does not directly cause neuronal loss. The defining feature of epilepsy is excessive brain neuronal excitability (not neuronal loss). The combination through Sweatt has proposed that increased activation of MAPK can reduce the excessive excitation of neurons that occurs in seizure disorder/epilepsy. The combination is said to teach using a c-Raf inhibitor to reduce MAPK activity to reduce neuronal excitability to treat seizure disorders. However, seizure disorders are not neurodegenerative disorders. The disorders used in the combination are simply not neurological disorders. The combination treats a totally different disease having different characteristics and symptoms. The present invention claims the use of c-Raf inhibitors to treat a different class of neurological disorders, specifically neurodegenerative disorders, of which epilepsy/seizure is not part of the disorder. Excessive neuronal excitability is not a feature of neurodegenerative diseases. On the contrary, patients with neurodegenerative diseases generally display sharply reduced brain neuronal activity.

The Office Action adds Varga to the combination. Varga relates to GW5074 and the involvement of Raf-1 in chronic o-opioid receptor activation agonist-mediated adenylyl cyclase superactivation. Adenylyl cyclase superactivation is not a neurodegenerative disease and there is nothing in the art that provides any indication that GW5074 provides any benefit other than in chronic o-opioid receptor activation agonist-mediated adenylyl cyclase superactivation. As such, the combination still fails to teach identifying a mammal having one or more apoptotic neuronal cells and administering to the mammal an effective amount of a C-Raf inhibitor that is a 3-substituted indolone. The combination still fails to disclose any treatment of a **neurodegenerative** disease.

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Amdt. Dated May 6, 2011  
Reply to Office Action of Jan. 20, 2011

Accordingly, claims 15, 17 and 23 are not anticipated by, or rendered obvious from Sweatt, Hall-Jackson and Varga, or any combination thereof. Applicant respectfully requests the Examiner withdraw the rejection under 35 U.S.C. § 103(a).

## CONCLUSION

In light of the foregoing, Applicant submits that claims 12, 14, 15, 17-35 are in condition for allowance, and an early Notice of Allowance of all pending claims is respectfully requested.

In view of the above, Applicant believes the pending Application is in condition for allowance. Applicant believes no fees are due with this response. However, if any additional fee is due, including those for an extension of time please charge any fees required or credit any overpayment to Chalker Flores, LLP's Deposit Account No. 50-4863 during the pendency of this Application pursuant to 37 CFR 1.16 through 1.21 inclusive, and any other section in Title 37 of the Code of Federal Regulations that may regulate fees. If an extension of time is required with this response but is not included, Applicant hereby petitions for a Request for Extension of Time under 37 CFR 1.136(a).

If the Examiner has any questions or comments, or if further clarification is required, it is requested that the Examiner contact the undersigned at the telephone number listed below.

Dated: May 6, 2011.

Respectfully submitted,



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Chainey P. Singleton  
Reg. No. 53,598

ATTORNEY FOR APPLICANT

Customer No. 34,725  
CHALKER FLORES, LLP  
14951 North Dallas Pkwy., Suite 400  
Dallas, Texas 75254  
214.866.0001 Telephone  
214.866.0010 Facsimile